ILSI Risk Science Institute

Model Peer Review Center of Excellence

POLICIES AND PROCEDURES

International Life Sciences Institute
Risk Science Institute
1126 Sixteenth St., NW
Washington DC 20036.

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INTERNATIONAL LIFE SCIENCES INSTITUTE

The **International Life Sciences Institute (ILSI)** is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. By bringing together scientists from academia, government, industry, and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public. Headquartered in Washington, D.C., ILSI is affiliated with the World Health Organization as a nongovernmental organization and has specialized consultative status with the Food and Agriculture Organization of the United Nations. ILSI accomplishes its work through its branches and institutes. ILSI's branches currently include Argentina, Australasia, Brazil, Europe, India, Japan, Korea, Mexico, North Africa and Gulf Region, North America, South Africa, South Andean, Southeast Asia, and Thailand, and a focal point in China. The ILSI Health and Environmental Sciences Institute focuses on global environmental issues.

The ILSI Research Foundation institutes include:
ILSI Allergy and Immunology Institute
ILSI Human Nutrition Institute
ILSI Risk Science Institute
The ILSI Center for Health Promotion comprises the Physical Activity and Nutrition Program and the Micronutrient Deficiency Program/Project IDEA (Iron Deficiency Elimination Action).

The ILSI Risk Science Institute (RSI) was established in 1985 to improve the scientific basis of risk assessment, the process by which scientists evaluate the risks to human health posed by man-made and natural substances in our living and working environments. Recognizing that public health decisions must be based on the best available science, RSI works toward this goal through an international program of working groups, conferences and workshops, publications, and seminars. RSI sponsors and participates in a wide range of activities to develop and disseminate new scientific knowledge, encourage exchange of ideas, and build consensus among scientists from academia, industry, government, and public interest groups.

RSI and its programs are supported by government grants, cooperative agreements, and contracts, as well as by contributions from the ILSI Research Foundation, other foundations, and private industry. RSI also provides scientific consultation to ILSI North America and ILSI Health and Environmental Sciences Institute Technical Committees and works with other ILSI branches on workshops and projects in risk assessment.

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ILSI Risk Science Institute

Model Peer Review Center of Excellence

POLICIES AND PROCEDURES

INTRODUCTION

The ILSI Risk Science Institute (ILSI RSI) has established an independent Model Peer Review Center of Excellence to evaluate toxicity assessments and associated proposed toxicity values for chemicals identified as contaminants of concern at Superfund hazardous waste sites. The Center has been created through a cooperative agreement between ILSI RSI and the EPA Office of Solid Waste and Emergency Response (OSWER).

With assistance and oversight by an external multi-sectoral Project Committee, ILSI RSI will organize and convene panels of nationally recognized experts to conduct independent critical reviews of the toxicity assessments and proposed toxicity values. The process will be open and transparent, and will solicit input from all stakeholders. Peer review results will be made available to the public. Peer reviews will be funded by sponsors who request the reviews.

OSWER will consider toxicity assessments and associated toxicity values that have been subject to review by the Model Peer Review Center of Excellence, for provisional usage in assessing baseline risks at Superfund sites, and will use peer-reviewed toxicity assessment documents submitted by sponsors as input to the EPA Integrated Risk Information System (IRIS) consensus review process.

Policies and procedures for the operation of the Model Peer Review Center were developed by ILSI RSI staff in consultation with the Project Committee. Policies and procedures include Peer Review Process; Process for Selection of Peer Reviewers; Conflict of Interest and Bias for Peer Review Panelists; Preliminary Information to be Provided by Potential Sponsors of Chemicals for Peer Review; and Toxicity Assessment Documents: Guidance for Sponsors.

These policies and procedures will be the guiding documents for RSI in undertaking this project. After the center has been in existence for approximately two years, an expanded Project Committee will evaluate the effectiveness and utility of the Model Peer Review Center and will prepare a report with recommendations on the scope, structure and function of future peer review centers of excellence, should they be needed. Further information on this project can be found on our website at www.ilsi.org/rsi/pr/index.html.

Please address letters of inquiry on this project to:

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Model Peer Review Center of Excellence Project

PEER REVIEW PROCESS

As a guiding principle, peer reviews conducted by the ILSI Risk Science Institute's Model Peer Review Center will be characterized by both *scientific integrity* and *process integrity*. Scientific integrity relates, for example, to the expertise and balance of the panel members, the identification of the scientific issues and clarity of the charge to the panel, the quality, focus, and depth of discussion of the issues by the panel, the rationale and supportability of the panel's findings, and the accuracy and clarity of the panel's report. Process integrity has to do with transparency and openness, avoidance of real or perceived conflicts of interest, a workable process for public comment and involvement, and defined procedures that are adhered to, with guidance and oversight by the Project Committee.

The formulation of the charge to the peer review panel is a critical step in the process. The charge to the panel will be developed by the Model Peer Review Center (PRC) staff, in consultation with the sponsors, the Project Committee, the chair of the panel, and other stakeholders if appropriate. Questions to be addressed by a peer review panel must be specific and clearly articulated. Examples might include, Does the toxicity assessment adequately describe and evaluate the available data? Does it acknowledge and address the relevant issues from prior evaluations of the chemical? Do the available data support the proposed toxicity value? What is the weight of evidence for/against the proposed value? What are the critical data gaps?

Peer review panel members will be highly qualified scientists drawn from multiple sectors, selected for their expertise in the requisite scientific disciplines and their experience in reviewing toxicity values. The peer review data package, including the toxicity assessment documents, charge to the panel, relevant literature, and other materials, will be sent to the peer review panel at least four weeks before the peer review panel meeting. At the same time, notice of the peer review panel meeting will be sent to stakeholders and interested parties, and the toxicity assessment executive summary submitted by the sponsors and charge to the panel established by the Model Peer Review Center will be posted on the Model Peer Review Center website (www.ilsi.org/rsi/pr/index.html).

Panel members will be asked to submit pre-meeting comments on the toxicity assessment documents for circulation within the panel. Prior to the meeting, PRC staff will arrange for a conference call of the panel chair and members to discuss the topic, the charge to the panel, pre-meeting comments from panel members, the process for the panel meeting, additional data sources and any potential conflict of interest or bias issues.

Peer review panel meetings typically will be one full day, held in the ILSI offices in Washington, DC. The meetings will be open to the public, and observers will be accommodated to the extent possible. ILSI RSI recognizes that it is in the public interest that an opportunity be

made available for all stakeholders to provide comments for consideration by the peer review panel. To that end, ILSI RSI will accept comments from the public on the toxicity assessment documents and proposed toxicity values and scientific issues to be addressed in the peer review. Written comments received at least 2 weeks before the panel meeting will be forwarded to the peer review panel in advance of the meeting. Written comments received thereafter will be made available to the panel at the meeting. On the day of the peer review, limited time will be provided for oral public comment, if requested in advance.

Panel meetings will begin with introduction of each of the panel members and declaration and discussion of any potential conflicts of interest. The chair will present and discuss the charge to the panel, and will lead and direct the discussions to ensure that the panel focuses on the questions comprising the charge. Sponsors may be invited to make a brief presentation on the toxicity assessment and the derivation of proposed toxicity values at the beginning of the meeting. Consensus conclusions will be sought on all issues. If there is significant disagreement on a question, the range of views and rationale for each will be presented in the panel's report.

The report of a peer review panel will be prepared by the panel chairman, with PRC staff support, and will be reviewed by the full panel prior to being finalized, then signed by the panel members. The toxicity assessment documents will be included as appendices to the peer review panel's report. The report will identify the members of the expert panel and their affiliations and will certify that conflict of interest statements were prepared and signed by all panel members, were reviewed and carefully considered by the PRC in selecting the panel, and that potential conflicts of interest were disclosed and discussed at the panel meeting.

The report of the peer review panel will be provided in a timely fashion by the PRC to the sponsors for their use. At the request of the sponsors, copies of the peer review panel report can also be provided directly to specified government agencies or other interested parties. The conclusions of the expert panel also will be made available to the public via the RSI Model Peer Review Center's website and in hard copy upon request.

Model Peer Review Center of Excellence Project

PROCESS FOR SELECTION OF PEER REVIEW PANEL MEMBERS

The ILSI Risk Science Institute Model Peer Review Center (PRC) will seek and accept nominations of experts from all stakeholders, including the Project Committee, federal and state government agencies, environmental and public interest groups, professional and trade associations, academia and the sponsors of the peer review. Nominations will be solicited by announcing the impending peer review on the Model Peer Review Center website (www.ilsi.org/rsi/pr/index.html), by direct contacts with potential stakeholders, and by other means as appropriate and feasible. The final selection of panel members will be solely the responsibility of the PRC staff. It is anticipated that, in most cases, there will be 7 to 9 peer reviewers on a panel. Alternate peer reviewers will be selected in the event that a panelist cannot serve.

Peer review panel members will be highly qualified scientists drawn from multiple sectors, selected for their expertise in the requisite scientific disciplines and their experience in reviewing toxicity values.

The chair of the panel will be a respected scientist and an experienced chair of technical peer review panels. He or she should have a thorough understanding of risk assessment principles and methods, as well as relevant expertise.

Peer reviewers will include scientists with general expertise in toxicology and risk assessment, as well as specialists in the specific endpoints of concern for the chemical to be reviewed. Reviewers' experience in conducting and evaluating hazard characterizations and familiarity with the risk assessment process will be considered. A balance of perspectives and affiliations also will be sought in panel selection.

Peer reviewers will be required to disclose any real or potential conflicts of interest or biases, as described in the Model Peer Review Center's Policy on Conflict of Interest and Bias, before being selected for a panel. Should a conflict of interest arise after selection, the panel member may be asked to resign. Names, affiliations and biographical sketches of panel members will be publicly available and posted on the Model Peer Review Center website.

Model Peer Review Center of Excellence

CONFLICTS OF INTEREST AND BIAS

It is the policy of the ILSI Risk Science Institute's Model Peer Review Center of Excellence that individuals selected to be peer review panel members will be free of conflicts of interest and biases that could result in partiality or loss of objectivity and compromise the work of the peer review panel. For these purposes, conflict of interest means any financial or other interest which conflicts with the service of an individual on a peer review panel because it (1) could impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization. Bias here refers to a prior view or position taken by an individual on the toxicity assessment or value under peer review, or on another assessment or chemical where the issue is very similar, or to a close association of the individual with the stated position or perspective of a particular group on the issue. These definitions are similar to those used by the National Research Council[1] and other organizations.

Potential conflicts of interest or biases, or the appearance of conflict of interest or bias, may be personal or may result from an individual's affiliations. Examples could include situations in which an individual:

- Has a direct or indirect financial interest in the outcome of the peer review process;
- Works for, or has recently worked for, a company that produces, uses, sells, or has other financial interests in the chemical under consideration;
- Has received research funding or consultant fees from a company that has financial interests in the chemical;
- Has testified in court on the chemical or the assessment under consideration;
- Is the author of the key research studies upon which toxicity assessment is based;
- Prepared the toxicity assessment documents that are to be peer reviewed; or
- Has been directly involved in developing or promulgating the government's toxicity value or similar government standard for the chemical.
- Has been associated with an organization that has taken a public position on the safety of the chemical under consideration.

Other examples could be cited[1,2].

To assist potential peer review panel members and the Model Peer Review Center (PRC) staff in identifying real or potential conflicts of interest or biases, or situations in which there may be the appearance of a conflict of interest or bias with regard to the chemical under consideration, all potential panel members must complete a standard questionnaire on Potential Sources of Conflicts of Interest and Bias (see attached). Completed questionnaires will remain confidential, with access restricted to the cognizant ILSI RSI PRC staff and legal counsel.

PRC staff will consider potential conflicts of interest and bias in selecting peer review panels (see *Process for Selection of Peer Review Panel Members*). Potential conflicts of interest will be discussed with the peer review panel prior to the panel meeting and will be discussed by

the panel in public at the beginning of the panel's peer review meeting. This discussion will be recorded in the final report of the peer review panel.

[1] – National Research Council Policy on Disclosure of Personal Involvements and Other Matters Potentially Affecting Committee Service, November 1, 1992.
[2] – Peer Review Handbook, EPA Science Policy Council, p. 47-48 (1998).

Model Peer Review Center of Excellence

CONFLICTS OF INTEREST AND BIAS QUESTIONNAIRE

Name_____

Employer_____

Address_____

_____

Phone_____Fax_____

E-mail _____

Peer Review Panel Assignment_____

In consideration of the stated policy of the ILSI RSI Model Peer Review Center of Excellence regarding conflict of interest and bias in peer review panels, please answer the following questions.

1. Do you have a financial interest in any company sponsoring the peer review? Please list. (For example, stocks, bonds, trusts, joint ventures, etc. The value of the interest need NOT be disclosed.)

2. Do you have a financial interest any other company that might benefit from the outcome of the peer review (including companies that hold the patent or manufacture the chemical under review or a competing chemical)? (For example, stocks, bonds, trusts, joint ventures, etc. The value of the interest need NOT be disclosed.)

3. Do you have any other direct financial stake in the outcome of the process?

4. List current sources of funding for your research and other significant professional activities, and previous funding over the past 4 years (use additional sheets if necessary).

5. Have you testified, made public statements, or taken positions relevant to the chemical under review? Please indicate the date, circumstances, and nature of the testimony, statement, or position. Provide the name of any organization with which you are closely associated or identified that has taken a position on this chemical and provide a brief description of the position.

6. Are you a current or recent employee (last 4 years) of a company that manufactures, uses, sells, or has other financial interest in the chemical being peer reviewed? Please specify.

7. Have you acted as a consultant for a company that might have a direct financial interest in the outcome of the peer review process? Please specify nature of consultancy and when it was completed or when it is scheduled for completion.

8. Are any of your scientific data likely to be considered as part of this peer review process? Please provide relevant citations.

9. Please provide any additional information that might be construed as a real or perceived conflict of interest that could affect your objectivity or the perception by others of your objective participation in the review.

I hereby declare that the disclosed information is true and accurate to the best of my knowledge, and that no other real, potential or apparent conflict of interest is known to me except as disclosed. I will promptly inform the ILSI RSI Model Peer Review Center of any change in these circumstances.

Name_____Signature_____

Date_____

Reviewed by

Name _____ Signature _____

Date_____

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PRELIMINARY INFORMATION TO BE PROVIDED BY POTENTIAL SPONSORS OF CHEMICALS FOR PEER REVIEW

Organizations interested in bringing a toxicity assessment and associated toxicity value(s) to the RSI Model Peer Review Center of Excellence are requested to provide the following preliminary information in a brief letter of inquiry:

1. The chemical involved
2. A brief summary of the rationale for the proposed peer review (key issues, toxicity values, etc.)
3. Existing toxicity values and assessments (e.g., IRIS Summary/Toxicological Review, RfDs/RfCs, etc.) for this chemical
4. Status of the toxicity assessment document proposed for review (which will provide a full discussion of the relevant literature): Has it been prepared? If not, what is the projected time frame for preparation of the document?
5. The sponsoring companies or other organizations and their respective interests in the chemical

Note that, in accordance with the terms of the cooperative agreement between RSI and the US Environmental Protection Agency Office of Solid Waste and Emergency Response, the chemicals that are the subject of peer reviews in this project must be found at one or more Superfund sites and must be of interest to multiple companies (as producers, users, potentially responsible parties (PRPs), etc.).

RSI will review the information provided and, in consultation with the Peer Review Center Project Committee, will determine if the proposed peer review can be conducted at the center.

Model Peer Review Center of Excellence Project

TOXICITY ASSESSMENT DOCUMENTS: Guidance for Sponsors

A high quality and comprehensive toxicity assessment data package based on a well designed and complete literature search is essential to a successful peer review. Toxicity assessment, in the context of this project, refers to hazard analysis/characterization (i.e., hazard identification and dose-response evaluation, including extrapolation methodology) applied to a specific substance. The toxicity assessment data package must present an in-depth, critical review and discussion of the available toxicity data for the chemical proposed for peer review and the rationale for any existing or proposed toxicity values associated with the chemical. Examples of toxicity values are reference doses (RfDs) or reference concentrations (RfCs), benchmark dose values, cancer slope factors, and others.

Sponsors of peer reviews are responsible for the preparation and submission of the necessary toxicity assessment documents. The scope of the submission will depend on the chemical, the database available on the substance, the toxicity values under consideration, and the sponsors' objectives for the peer review. For example, if a new RfD is proposed as part of the toxicity assessment, the toxicity assessment document will need to cover in some detail the full toxicity database for the chemical to demonstrate that the critical effect selected is appropriate. If the focus is on the re-evaluation of a cancer slope factor, the discussion of the data pertinent to carcinogenicity (studies of cancer and pre-neoplastic effects in animals and humans, mode of action, genotoxicity, etc.) may be more extensive. However, in any case, the toxicity assessment should present a comprehensive overview and characterization of the toxicity of the chemical.

Following the peer review, the sponsors may wish to submit the toxicity assessment and the report of the peer review panel directly to a regulatory agency. If so, the scope and content of the assessment documents should take account of the needs of the regulatory agency. For example, if the toxicity assessment is intended to support an EPA IRIS update, the sponsors should consult the IRIS website (http://www.epa.gov/iris) for examples of recent IRIS Summaries and Toxicological Reviews. In addition, as a matter of policy, the EPA Office of Solid Waste and Emergency Response (OSWER) has stated that it "does not intend to accept privately generated toxicity assessment documents and associated values for possible provisional usage and for nomination into the Integrated Risk Information System (IRIS) consensus process, unless complete reviews of the available data on the toxicity of the chemicals are presented in the submitted documents."

The toxicity assessment data package should include:

- A cover letter that identifies the chemical and certifies that it has been found at Superfund sites, identifies the sponsoring companies or other organizations and their respective

interests in the chemical, specifies the toxicity assessment and associated toxicity values to be peer reviewed, and proposes questions to be addressed by the peer review panel.

- The toxicity assessment document. As noted above, the scope and content of this document will depend on several factors. In general, it should include the following components:
    1. Executive Summary (overview of the toxicity and hazard analysis of the chemical, including the rationale and derivation of any newly proposed toxicity values and comparison with existing values)
    2. Chemical data relevant to the assessment
    3. Hazard identification (review and discussion of human and animal data relevant to the evaluation, selection of critical effect(s) and studies, discussion of other effects, evidence for mode(s) of action, consideration of possible susceptible populations)
    4. Dose-response assessment (review and discussion of available data, selection of method(s) of analysis, detailed description of derivation of the proposed toxicity value)
    5. Overall discussion and conclusions (including comparison of any proposed toxicity values with published values, discussion of assumptions, uncertainties and data gaps, remaining issues and ongoing studies)
    6. Reference list (and the literature search strategy)
- Copies of the references cited in the toxicity assessment document

It is recommended that the list of pertinent references and the literature search strategy used be submitted to the RSI Peer Review Center (PRC) for review prior to submission of the toxicity assessment. Since some or all of the material in the toxicity assessment data package could be made available to the public, sponsors are advised not to include data considered to be proprietary or confidential.

The RSI PRC staff welcomes sponsor inquiries and discussion on the content and format of toxicity assessment documents and ancillary materials. The toxicity assessment data package should be submitted after it has been agreed that the proposed peer review is appropriate for the Model Peer Review Center of Excellence Project (see *Preliminary Information to be Provided by Potential Sponsors of Chemicals for Peer Review*, on the RSI Peer Review Center website at http://www.ilsi.org). PRC staff will review the toxicity assessment data package and may request clarifications or additions, if necessary.

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PROJECT COMMITTEE

Frank Baker	Procter & Gamble (ret.)
John Bucher	NIEHS/National Toxicology Program
Joan Denton	California Office of Environmental Health Hazard Assessment
Chris DeRosa	Agency for Toxic Substances and Disease Registry, CDC
Ronald Estabrook (Chair)	Southwestern Medical Center, University of Texas
Bernard Goldstein	EOHSI, UMDNJ-Robert Wood Johnson Medical School
Carol Henry	American Chemistry Council (formerly CMA)
Steven Lewis	Exxon Biomedical Sciences
Paul Locke	Pew Environmental Health Commission at Johns Hopkins University
Dorothy Patton	EPA Science Policy Council (ret.)
Bernard Schwetz	Food and Drug Administration
Susan Sieber	National Cancer Institute
Ellen Silbergeld	University of Maryland School of Medicine
Robert Rickard	E.I. DuPont de Nemours & Co.
Vanessa Vu	EPA National Center for Environmental Assessment